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# Allele Variants of the Cytochrome P450 2C9 Genotype in White Subjects from The Netherlands with Serious Gastroduodenal Ulcers Attributable to the Use of NSAIDs

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## ABSTRACT

**Background:** The most common serious adverse effects (AEs) associated with NSAID therapy are bleeding and perforated gastroduodenal ulcers. These AEs are dose related, and reduced oral clearance of NSAIDs associated with polymorphisms of cytochrome P450 (CYP) would, theoretically, increase the risk for AEs.

**Objective:** The purpose of this study was to determine whether polymorphisms of the CYP2C9 genotype are associated with the development of serious complications of NSAID-related ulcers.

**Methods:** We examined the records of patients with complications of serious NSAID-related ulcers who were hospitalized from November 2001 to December 2003. Diagnosis was confirmed by endoscopy or abdominal surgery, and a group of consecutive subjects was identified for genetic analysis. CYP2C9 allele frequencies were determined and compared with those in a matched cohort of subjects receiving stable weekly maintenance doses of oral coumarin anticoagulants. Allele frequencies also were compared with those in matched cohorts from earlier studies.

**Results:** All 26 subjects with serious NSAID-related ulcers were white, 15 (58%) were female, and the median age was 74.5 years (range, 32–96 years). All 87 subjects in the reference group were white, 24 (28%) were female, and the median age was 69 years (range, 48–81 years). CYP2C9 genotype frequencies did not differ significantly between subjects with serious complications of NSAID-related ulcers and subjects using oral coumarin anticoagulants. The genotype frequencies in both groups were similar to those reported in previous studies in white subjects.

**Conclusion:** The CYP2C9 genotype was not a significant or clinically relevant risk factor in the development of serious NSAID-related ulcers in this group of subjects. (*Clin Ther.* 2006;28:1670–1676) Copyright © 2006 Excerpta Medica, Inc.

**Key words:** NSAID, ulcer, cytochrome P450, polymorphism.

## INTRODUCTION

NSAIDs are among the most frequently prescribed medications in the world, with ~30 million people using them on a daily basis.<sup>1</sup> Bleeding and perforated gastroduodenal ulcers are among the most serious complications of NSAID therapy and may lead to significant morbidity, mortality, and financial costs. Among chronic NSAID users, the annual incidence of serious NSAID-related ulcers requiring treatment and hospitalization is estimated at 1% to 2%, with an associated mortality rate of 10% to 15%.<sup>2–4</sup> In The Netherlands, the annual direct medical costs of the complications of serious NSAID-related ulcers have been estimated to be more than €42 million.<sup>4</sup>

Several additional risk factors for NSAID-related ulcers have been identified, including advanced age, history of ulceration, and *Helicobacter pylori* infection.<sup>5,6</sup> The risk of NSAID-related ulcers is influenced by the type of NSAID, dose, and use of >1 NSAID

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simultaneously.<sup>7-9</sup> Concomitant use of other drugs, such as steroids, anticoagulants, platelet inhibitors, and selective serotonin reuptake inhibitors, may further increase the risk for serious ulcers.<sup>10,11</sup> Coexisting systemic disorders, such as diabetes mellitus and debilitating rheumatic diseases, also have been identified as risk factors.<sup>12</sup> In daily clinical practice, however, serious complications of NSAID-related ulcers also may be seen in subjects who lack obvious risk factors (ie, subjects aged <60 years who are otherwise healthy). It is possible, therefore, that other unidentified risk factors for NSAID-related ulcers exist.

The cytochrome P450 (CYP) system is a large group of hemoproteins that catalyze the metabolism of many different chemicals. In humans, most drugs are activated and detoxified by 4 CYP families (CYP1, CYP2, CYP3, and CYP4).<sup>13</sup> The CYP2C9 isozyme has been found to catalyze at least part of the metabolism of a number of drugs, including warfarin, tolbutamide, losartan, phenytoin, and at least 16 different NSAIDs, including acetylsalicylic acid, celecoxib, diclofenac, flurbiprofen, ibuprofen, indomethacin, meloxicam, and naproxen.<sup>14</sup> Apart from the wild-type protein, CYP2C9\*1, at least 5 CYP2C9 genetic polymorphisms with reduced metabolic activity have been observed.<sup>15,16</sup> Two of these variants, CYP2C9\*2 and CYP2C9\*3, appear to have significant functional effects and have been found in relatively high frequencies in the white population, although they seem to be much less prevalent in other racial groups.<sup>17-19</sup> In other studies, the CYP2C9\*4 variant was found in Japanese subjects but not in white subjects; the CYP2C9\*5 variant was found in black and Hispanic subjects but not in white subjects; and the CYP2C9\*6 variant was found in 1 black subject who experienced drug toxicity after receiving normal doses of phenytoin.<sup>19,20</sup>

The normal functioning wild-type of CYP2C9, CYP2C9\*1, has been reported to have a population frequency of 65% in white subjects, 87% in black subjects, and 96% in Asian subjects.<sup>17,18,21,22</sup> The CYP2C9\*2 allele has a single base substitution at position 144, which results in a change from arginine to cysteine. Subjects with the heterozygous CYP2C9\*1/\*2 genotype appear to exhibit a minor reduction in catalytic activity of the CYP2C9-encoded enzyme. Studies have reported high population frequencies of this genotype in white (20.4%) and black (8.7%) subjects but not in Asian subjects (0%). A moderate reduction in the functional activity of

CYP2C9 has been noted in subjects with the homozygous CYP2C9\*2/\*2 genotype, but the population frequency of the CYP2C9\*2/\*2 genotype is much lower (0.9% in white subjects and 0% in black and Asian subjects). The CYP2C9\*3 allele has a single base substitution at position 359, which results in an amino acid change from isoleucine to leucine. The catalytic activity of the CYP2C9\*3-encoded enzyme appears to be much lower than that of enzymes encoded by the wild-type, CYP2C9\*1. Subjects with the heterozygous CYP2C9\*1/\*3 genotype and those with the compound heterozygous CYP2C9\*2/\*3 genotype appear to exhibit a moderate reduction in catalytic activity. The population frequency of the CYP2C9\*1/\*3 genotype has been reported as 11.6% in white subjects, 4.3% in black subjects, and 3.5% in Asian subjects, whereas the population frequency of the CYP2C9\*2/\*3 genotype has been reported as 1.4% in white subjects and 0% in black and Asian subjects.<sup>17,18,21,22</sup> The homozygous CYP2C9\*3 genotype is associated with a very low level of catalytic activity, and the frequency of the CYP2C9\*3/\*3 variant has been reported to be only 0.4% in white subjects and 0% in black and Asian subjects.<sup>17,18,21,22</sup>

CYP2C9 polymorphisms have been associated with changes in the pharmacokinetics of some frequently used NSAIDs.<sup>17-19,23</sup> Relative to subjects with the homozygous CYP2C9\*1 genotype, oral clearance of celecoxib was reduced by 77% in subjects with the homozygous CYP2C9\*3 genotype and by 32% in subjects with the heterozygous CYP2C9\*3 genotype. Oral clearance of ibuprofen was reduced by 45% in subjects with the homozygous CYP2C9\*3 genotype and by 28% in subjects with the heterozygous CYP2C9\*3 genotype. Oral clearance of diclofenac was reduced by 14% in subjects with the homozygous CYP2C9\*3 genotype and by 5% in subjects with the heterozygous CYP2C9\*3 genotype. Among homozygous and heterozygous CYP2C9\*2 subjects, oral clearance of celecoxib and diclofenac was similar or even greater than the clearance in those with the wild-type, CYP2C9\*1. However, for ibuprofen, subjects with the homozygous CYP2C9\*2 genotype had a 22% reduction in oral clearance, and heterozygous subjects had a 12% reduction.

Serious adverse events associated with NSAID therapy, such as bleeding and perforated gastroduodenal ulcers, are dose related, which raises the question of whether the reduced NSAID clearance associated with

CYP2C9 polymorphisms may increase the risk of serious NSAID-related gastroduodenal ulcers. If so, CYP2C9 allele frequencies would be expected to differ from those in the general population. To test this hypothesis, we examined CYP2C9 allele frequencies in a group of white subjects from The Netherlands with serious NSAID-related ulcers and compared them with frequencies in a group of matched control subjects using oral coumarin anticoagulants and with those reported in white subjects in earlier studies.<sup>17</sup>

## SUBJECTS AND METHODS

### Subjects

Serious NSAID-related ulcers were defined in this study as ulcerations of the stomach or proximal duodenum causing pain, perforation, obstruction, or bleeding that occurred during the time the subject was taking NSAIDs and resulted in treatment and hospitalization. We identified all consecutive subjects with serious gastroduodenal ulcers who were hospitalized at the Medisch Spectrum Twente Hospital in Enschede, The Netherlands, from November 2001 through December 2003. The diagnosis was confirmed by endoscopy or abdominal surgery. If diagnostic procedures were not performed because of comorbidity or advanced age, subjects with gastroduodenal ulcers were identified on the basis of a clinical presentation of upper gastrointestinal bleeding with hematemesis or melena. In a few subjects, the diagnosis was confirmed during autopsy. Subjects were eligible for inclusion if they reported using an NSAID at any time up to the diagnosis of a gastroduodenal ulcer.

Subjects were excluded if written informed consent could not be obtained, if they reported not having used NSAIDs, if endoscopy or surgery did not reveal gastric or duodenal ulcers, if a malignancy of the stomach was found, or if another cause was determined for upper intestinal bleeding (eg, diffuse gastritis, esophagogastric varices, arteriovenous malformations, or Mallory-Weiss tears).

CYP2C9 allele frequencies also were determined in a matched cohort of subjects using oral coumarin anticoagulants at stable weekly maintenance doses under supervision of the Thrombosis Services at the Medisch Spectrum Twente Outpatient Clinic in Oldenzaal, The Netherlands.

The study was approved by the Medical Ethics Reviewing Committee of the Medisch Spectrum Twente Hospital, Enschede, The Netherlands.

### Methods

CYP2C9 genotyping was performed using a standard polymeric chain reaction technique with relevant test controls. This technique has been described in an earlier study of genetic polymorphism.<sup>24</sup>

CYP2C9 allele frequencies were compared using the Pearson  $\chi^2$  test, and, in cases in which the expected values were low, the Fisher exact test was used. All analyses were performed using SPSS for Windows, version 12.0.1 (SPSS Inc., Chicago, Illinois).

Based on previous studies of allele variants,<sup>17-19,23</sup> we assumed that the presence of the variant allele CYP2C9\*2 or CYP2C9\*3 would increase a subject's risk for serious NSAID-related gastroduodenal ulcers. Based on previously published frequency data for this population, we expected ~35% (30/87) of the subjects in the reference group to have variant alleles. Assuming a ratio of ~3 for the comparison of reference subjects and subjects with serious NSAID-related ulcers, a power of 80%,  $\alpha = 0.05$ , and an odds ratio of 3, we calculated that it would be necessary to examine CYP2C9 allele frequencies in 35 subjects with serious NSAID-related gastroduodenal ulcers.

### RESULTS

A cohort of 26 consecutive subjects with serious NSAID-related ulcers was selected for CYP2C9 allele analysis. All subjects were white, 15 (58%) were female, and the median age was 74.5 years (range, 32-96 years). Eleven (42%) of the subjects used diclofenac, 4 (15%) used ibuprofen, 4 (15%) used naproxen, 4 (15%) used rofecoxib, 2 (8%) used diclofenac/misoprostol, and 1 (4%) used meloxicam (Table I). Seven (27%) patients used more than the maximum recommended dose of NSAID, and 5 (19%) used >1 NSAID concurrently. Concomitant use of low-dose aspirin was reported by 6 (23%) subjects, coumarin derivatives by 5 (19%), steroids by 4 (15%), low-molecular-weight heparin by 2 (8%), and selective serotonin reuptake inhibitors by 1 (4%). Five (19%) subjects used either proton pump inhibitors or high-dose histamine<sub>2</sub>-receptor antagonists. Only 1 subject had a history of gastroduodenal ulcers. Testing for *H pylori* was performed on biopsy specimens from the gastric mucosa of 20 subjects by histologic examination using hematoxylin and eosin staining and immunohistochemical *H pylori* antibody staining. The results were positive in 5 (25%) subjects.

**Table I.** Characteristics of white subjects with serious NSAID-related ulcers by sex, age, weight, NSAID type, dose, expected effect of CYP2C9 genotypes on NSAID pharmacokinetics, and CYP2C9 genotype.

Subject	Sex	Age, y	Weight, kg	NSAID	Dose*	Expected Effect of CYP2C9 Genotype†	CYP2C9 Variant
1	M	79	75	Diclofenac/ misoprostol	Medium	Minor	*1/*1 (wild-type)
2	F	89	60	Diclofenac/ misoprostol	Medium	Minor	*1/*1 (wild-type)
3	F	78	45	Diclofenac	Medium	Minor	*1/*3 (heterozygous)
4	M	62	77	Diclofenac	Low	Minor	*1/*1 (wild-type)
5	M	73	103	Diclofenac	Medium	Minor	*1/*1 (wild-type)
6	F	48	78	Diclofenac	Low	Minor	*1/*1 (wild-type)
7	M	76	60	Diclofenac	Medium	Minor	*1/*2 (heterozygous)
8	M	64	77	Diclofenac	High	Minor	*1/*2 (heterozygous)
9	M	70	75	Diclofenac	High	Minor	*1/*3 (heterozygous)
10	F	86	56	Diclofenac	Low	Minor	*1/*1 (wild-type)
11	M	32	103	Diclofenac	Low	Minor	*1/*2 (heterozygous)
12	M	63	100	Diclofenac	Medium	Minor	*1/*1 (wild-type)
13	F	75	69	Diclofenac	Low	Minor	*1/*1 (wild-type)
14	F	59	58	Ibuprofen	Low	Major	*1/*1 (wild-type)
15	M	50	53	Ibuprofen	Low	Major	*1/*2 (heterozygous)
16	F	93	55	Ibuprofen	High	Major	*1/*1 (wild-type)
17	F	36	63	Ibuprofen	Low	Major	*1/*1 (wild-type)
18	F	89	89	Meloxicam	Medium	Major	*1/*1 (wild-type)
19	F	80	101	Naproxen	High	Minor	*1/*1 (wild-type)
20	M	68	106	Naproxen	High	Minor	*1/*1 (wild-type)
21	F	82	59	Naproxen	High	Minor	*1/*2 (heterozygous)
22	F	60	56	Naproxen	Low	Minor	*1/*1 (wild-type)
23	M	74	95	Rofecoxib	High	Minor	*1/*1 (wild-type)
24	F	89	61	Rofecoxib	Low	Minor	*1/*1 (wild-type)
25	F	82	60	Rofecoxib	Medium	Minor	*1/*2 (heterozygous)
26	F	96	60	Rofecoxib	Medium	Minor	*1/*2 (heterozygous)

CYP = cytochrome P450; M = male; F = female.

\*Medium = recommended maximum daily dose; low = less than the recommended maximum daily dose; high = more than the recommended maximum daily dose.

†Derived from Scordo et al.<sup>21</sup>

A cohort of 87 consecutive subjects using oral anti-coagulants also was selected for CYP2C9 allele analysis. All subjects were white, 24 (28%) were female, and the median age was 69 years (range, 48–81 years).

The CYP2C9 genotype frequencies for the subjects with serious NSAID-related ulcers, the subjects using oral coumarin anticoagulants, and subjects in previous studies are shown in Table II. CYP2C9 genotype frequencies did not differ significantly between the subjects with serious NSAID-related ulcers and the

subjects using oral anticoagulants. The genotype frequencies in both groups were similar to those in white subjects in previous studies.<sup>17</sup>

In subjects with serious NSAID-related ulcers, the genotype frequencies were 65% for CYP2C9\*1/\*1 (Arg<sub>144</sub>-Ile<sub>359</sub>, wild-type), 27% for CYP2C9\*1/\*2 (Cys<sub>144</sub>-Ile<sub>359</sub>), and 8% for CYP2C9\*1/\*3 (Arg<sub>144</sub>-Leu<sub>359</sub>). The homozygous CYP2C9\*2/\*2 genotype and the homozygous CYP2C9\*3/\*3 genotype were not found in the subjects with serious NSAID-related

Table II. *CYP2C9* polymorphisms in white subjects with serious NSAID-related ulcers and subjects using oral coumarin anticoagulants (no. [%] of subjects), and in the historical subjects (no.).

Allele Variant	Subjects with Serious NSAID-Related Ulcers (n = 26)	Subjects Using Oral Coumarin Anticoagulants (n = 87)	Historical Cohort <sup>17</sup> (N = 100)
<i>CYP2C9</i> *1/*1 (wild-type)	17 (65)	56 (64)	65
<i>CYP2C9</i> *1/*2 (heterozygous)	7 (27)	12 (14)	20
<i>CYP2C9</i> *2/*2 (homozygous)	0	0	1
<i>CYP2C9</i> *1/*3 (heterozygous)	2 (8)	14 (16)	12
<i>CYP2C9</i> *2/*3 (compound)	0	5 (6)	1
<i>CYP2C9</i> *3/*3 (homozygous)	0	0	0

CYP = cytochrome P450.

ulcers or in subjects receiving oral anticoagulants. The compound heterozygous *CYP2C9*\*2/\*3 genotype was not found in subjects with serious NSAID-related ulcers, but it occurred at a frequency of 6% in subjects using oral anticoagulants (Table II).

## DISCUSSION

The results of this study suggest that in these white subjects living in The Netherlands, allele variants of the *CYP2C9* genotype were not a clinically relevant risk factor for serious NSAID-related gastroduodenal ulcers.

One possible weakness of this study is that we compared consecutive subjects from 2 different cohorts, the first consisting of subjects with serious NSAID-related gastroduodenal ulcers and the second consisting of subjects using oral anticoagulants. Since it is possible that the 2 groups may not have been comparable in terms of the risk for bleeding, we compared the genotype frequencies in these subjects with frequencies reported in previous studies.<sup>17</sup>

Neither the homozygous *CYP2C9*\*2/\*2 genotype, the homozygous *CYP2C9*\*3/\*3 genotype, nor the compound heterozygous *CYP2C9*\*2/\*3 genotype was found in the subjects with serious NSAID-related ulcers. Twice as many subjects with a heterozygous *CYP2C9*\*1/\*3 genotype were found among the subjects using oral anticoagulants as in the subjects with serious NSAID-related ulcers. This suggests that, at the population level, the *CYP2C9* genotype is not likely to be a clinically relevant risk factor for the development of serious NSAID-related ulcers.

Another possible weakness of this study is that some of the subjects used more than the maximum recommended daily doses of NSAIDs, and others used less than the maximum recommended doses. Also, the *CYP2C9* genotype plays only a small role in the overall clearance of some of the NSAIDs used by the subjects.<sup>25</sup> Because the serious adverse effects associated with NSAID therapy, such as bleeding and perforated gastroduodenal ulcers, are dose related, it is possible that the lack of association with *CYP2C9* genotypes in this study is related to the types and doses of NSAIDs used by the subjects.

The subjects with serious NSAID-related ulcers in this study were representative of the subjects seen in clinical practice; thus, at the population level, the *CYP2C9* genotype is not likely to be a clinically relevant risk factor. In an individual subject who is a poor metabolizer, however, high doses of NSAIDs whose clearance is influenced by *CYP2C9* may increase the risk for serious NSAID-related ulcers. Future case-control studies may answer this question by determining *CYP2C9* allele frequencies in subjects with and without bleeding gastroduodenal ulcers who use NSAIDs.

Previous studies have examined the role of genotype frequencies in the development of NSAID-related ulcers. In one case-control study in 23 white subjects with previous NSAID gastropathy and 32 asymptomatic control subjects who used NSAIDs, no significant difference in *CYP2C9* allele frequencies was found.<sup>26</sup> In a larger Spanish case-control study in 94 subjects with NSAID-attributable gastrointestinal bleeding and

124 asymptomatic control subjects who used NSAIDs, the subjects with serious NSAID-related ulcers were significantly more likely to be carriers of the variant CYP2C9\*2 allele ( $P < 0.01$ ) but not of the low-metabolizing CYP2C9\*3 allele.<sup>27</sup>

Although CYP2C9 polymorphisms do not appear to play a significant role in the development of NSAID-related ulcers, their effect may be different in subjects who use other drugs concomitantly. Several drugs are known to or can be expected to further increase the risk for NSAID-related ulcers. These include drugs that pharmacodynamically influence blood coagulation, such as platelet inhibitors, low-dose aspirin, clopidogrel, and dipyridamole, and drugs whose pharmacokinetics are influenced by the CYP2C9 isozyme either competitively, as in the case of selective serotonin reuptake inhibitors and coumarin anticoagulants, or by inhibition of the CYP2C9 isozyme, as in the case of benzbromarone and amiodarone. Also, the mechanism by which some drugs, such as corticosteroids, increase the risk for NSAID-related ulcers is not completely understood. Subjects who are prescribed combined therapy with NSAIDs and coumarin anticoagulants are at increased risk of bleeding.<sup>28</sup> The CYP2C9 isozyme catalyzes the metabolism of NSAIDs and coumarin anticoagulants, and poor metabolizers who are prescribed this combination may be at particular risk for bleeding. Several studies have found an association between CYP2C9 genotypes and coumarin dose requirements<sup>29,30</sup>; however, studies of the effect of CYP2C9 polymorphisms on the NSAID-coumarin interaction have had conflicting results.<sup>31,32</sup> This conflict may be explained by the difference in study designs (prospective vs retrospective) and the numbers of subjects included in the trials. In our study, only 5 subjects used an NSAID and coumarin concomitantly. Four of these subjects had the CYP2C9\*1/\*1 variant genotype and 1 subject had the CYP2C9\*1/\*2 variant. Future case-control studies may resolve this conflict by comparing CYP2C9 allele frequencies in subjects with bleeding NSAID-related gastroduodenal ulcers who are using NSAIDs and coumarin derivatives concomitantly and those in subjects using both drugs without bleeding complications.

## CONCLUSION

In this group of white subjects from The Netherlands, allele variants of the CYP2C9 genotype were not a

significant or clinically relevant risk factor for serious NSAID-related gastroduodenal ulcers.

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